PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chia-Gee **WANG**, et al.

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For: RADIOTHERAPY METHOD USING X-RAYS

Attorney Docket No.: **U 014775-5**

Commissioner for Patents
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APPEAL BRIEF

This Appeal Brief is submitted further to the Notice of Appeal filed on 15 July 2010.

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I. REAL PARTY IN INTEREST

The real party in interest is Nanodynamics, Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, judicial proceedings, or interferences known to Appellant which are related to directly affect or are directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 3, 5, 7, 12, 16-24, 26-36, 38, 40, 42, 47, 51-59, 61-65, 67, 69, 71, 76-88, 90, 92, 97 and 99 are finally rejected and are being appealed.

IV. STATUS OF AMENDMENTS

No amendments after final have been filed.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1

The invention defined by claim 1 is a method for the **preferential** disruption of malfunctioning cells. The method comprises the steps of

(a) administering a compound which associates with DNA in cells of a mammal, the compound comprising a pre-selected element selected from the group consisting of Pt, Ca, Ti, Br, I Gd, Y and Ru (specification at, e.g., paragraphs [0025]-[0026], [0029]-[0030], Table 2 on page 14); and

(b) irradiating a selected region in which malfunctioning cells having the compound associated with DNA are located, with line emission x-rays (specification at paragraphs [0022] and [0033]). The line emission x-rays are of an energy selected to cause

emission of Auger electrons from the pre-selected element in a dose effective to disrupt DNA proximate to the irradiated pre-selected element (within a distance of a few atomic diameters from the pre-selected element) so as to localize the effects of disrupting DNA to the malfunctioning cells and to minimize the effect on normal cells. See specification at paragraphs [0023] and [0029]. See, also, specification at paragraph [0009] ("The x-ray beam provides the ability to localize the release of Auger electrons to eliminate cancerous, tumorous or malfunctioning cells with minimum damage to other normal body tissues.").

In accordance with the claimed method, the use of bright x-ray beams of defined line emissions tuned to the absorption edge of a selected element (e.g., platinum) in a compound associated with malfunctioning cells provides the ability to cause the emission of Auger electrons from the selected element in a dose of at least 10^6 Gy within a few atomic distances from the selected element. This causes disruption of the DNA and death of the cells containing the selected element, **with localization of the damage to such cells so as to avoid destroying healthy tissue**.

Claim 85

The method defined by claim 85 is a method for treating malfunctioning cells in a living mammal, which comprises the steps of:

(a) providing a kit comprising

(1) an x-ray tube having a target comprising a selected metal, which tube is capable of emitting monochromatic line emission x-rays (specification at paragraphs [0045] - [0047]);

(2) a compound comprising a selected element selected from the group consisting of Pt, Ca, Ti, Br, I, Gd, Y and Ru that is capable of associating with DNA in cells of the mammal (specification at, e.g., paragraphs [0025]-[0026], [0029]-[0030], Table 2 on page 14), wherein the selected metal of the target and the selected element of the compound are selected together such that the metal of the target emits line emission x-rays having an energy above and near the K-absorption edge or the L-absorption edge of the selected

element (specification at paragraphs [0033] and Table 2 on page 14), which causes the selected element to release a dose of Auger electrons upon irradiation by the line emission x-rays in a dose (at least 10^6 Gy) effective to disrupt DNA within a few atomic diameters of the irradiated selected element (specification at paragraphs [0009], [0023] and [0029]);

(b) administering the compound to the mammal (specification at paragraph [0025]); and

(c) irradiating a selected region in which malfunctioning cells having the compound are located with the monochromatic line emission x-rays to cause emission of Auger electrons from the pre-selected element in the dose effective to disrupt DNA proximate to the irradiated pre-selected element (specification at paragraphs [0009], [0023] and [0030]).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether Claims 1-12 amd 15-25 are unpatentable under 35 U.S.C. 103(a) over Mills (U.S. Patent 6,224,848) in view of Wang (U.S. Patent 5,627,871).

VII. ARGUMENT

The claimed invention is based at least in part upon Applicant's discovery that, with the use of bright x-ray beams of defined line emissions tuned to the absorption edge of a selected element (e.g., platinum) in a compound associated with malfunctioning cells, it is possible to cause the emission of Auger electrons from the selected element associated with DNA of irradiated cells in a dose of at least 10^6 Gy *in situ* within a few atomic distances from the selected element. This causes the disruption of the DNA and death of the cells, while localizing the damage to such cells (specification at, e.g., paragraphs [0009], [0023] and [0029]). The sphere of damage is so localized (a few atomic distances) that it would be harmless everywhere in a cell except the DNA of the cell such that the Auger cascade can be used to destroy malfunctioning cells without destroying other cells outside of a very small ionization sphere.

This is explained in greater detail in the Declaration under 35 USC 1.132 of Dr. C.G. Wang filed 2 June 2009. As discussed in the declaration, the Auger electrons from an Auger cascade caused by irradiating the cells with line emission x-rays tuned to the K-absorption edge of the selected element deliver 10^6 Gray in a very small ionization sphere. This sphere of damage is so localized (a few atomic distances) that it would be harmless everywhere in a cell except the DNA in the cell. Thus, the Auger cascade can be used to destroy the cells without destroying other cells outside of the very small ionization sphere.

In accordance with this discovery, all claims of record recite a step of irradiating a selected region, in which malfunctioning cells comprising a compound with the selected element associated with DNA of the malfunctioning cells are located, with line emission x-rays so as to cause emission of Auger electrons in a dose of at least 10^6 Gy *in situ* within a few atomic distances from the selected element whereby to localize the effects of disrupting DNA to the malfunctioning cells.

In contrast, the primary reference, Mills, teaches a therapy that relies upon Mossbauer absorption as opposed to radiation with x-rays. As explained in the Wang Declaration, the emission and absorption of gamma-rays in a solid under the Mossbauer effect initiated by a nuclear decay is very different from the Auger cascade and the Auger dose initiated by a controlled external photon beam as claimed. In Mills, the **nuclei** of administered isotopes at the target tissue absorb gamma rays and undergo an internal conversion, which is followed by an Auger electron cascade (see Mills at Abstract and claim 5). In the claimed invention, an Auger cascade commences when the atom, not the nucleus, has an inner shell ionization caused by K-edge or L-edge absorption initiated by a controlled external photon beam which leads to a number of low energy Auger electrons in a cascade whose kinetic energy is between 12-18 eV with a range of 5-10 atomic dimensions in water (Wang Declaration at paragraphs 4-7). Mills does not show or suggest the use of a controlled external irradiation source to induce a large radiation dose *in situ* next to a target atom.

One of ordinary skill in the art would have had no reason or motivation to substitute the claimed line emission x-rays for the gamma-rays of Mills. To the contrary, the principle of operation described in Mills is tied to "a radiation source which provides **energy**

at the corresponding resonant Mossbauer absorption frequency of isotope containing pharmaceutical" (emphasis added). Mills at Abstract; see, also, column 2, lines 45 -50 ("The excitation is by a radiation source, the apparatus of the invention, at the corresponding resonant Mossbauer absorption frequency of selected tissue having received the administered pharmaceutical where excitation effects nuclear transitions to cause selective energy absorption in the selected target tissue."), and column 5, lines 7-13 ("Therefore, treatment is carried out by irradiating the selected tissue with gamma radiation of the proper energy and polarization and gamma ray propagation direction to match the conditions for resonant absorption by the Mossbauer absorber isotope atoms of the pharmaceutical molecules present in the target selected tissue.").

There is nothing in Mills that would show or suggest if or how the method described therein could be modified to create an Auger cascade other than by Mossbauer absorption using gamma rays of a corresponding Mossbauer absorption frequency. Moreover, there could have been no reason or motivation to modify Mills in the manner suggested by the Examiner as this would improperly change the principle of operation of the reference. See MPEP 2143.01(VI) ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.").

In any event, Mills would not have provided even a reasonable expectation of success with the claimed method since one of ordinary skill in the art could not have expected that the use of **external x-rays** generating the claimed dose of 10^6 Gy *in situ* could be made without unacceptable damage to a patient. Indeed, prior art patents dealing with radiosurgery from an external x-ray source teach away from this. For example, Cash et al US Patent 6,366,801 describes radiosurgery with the use of a heavy element contrast agent in connection with a monochromatic x-ray source with distinct and specific frequency and energy level properties (see Cash at column 8, line 46 to column 9, line 39 ("Optimized X-ray Spectrum")). Cash teaches that it is necessary to limit the radiation to a dose that is orders of magnitude less than the claimed dosage of 10^6 Gy *in situ*. See Cash et al at, e.g., column 12, lines 43-48 ("a preferred approach is to irradiate the patient 10 so that the tumor receives 1600 cGy in a single dose, and the surrounding healthy tissue receives 1600/de

cGy."); see, also, Cash at column 15, Example 1 ("At the skin, a dose of 10 Gy accumulates, which is **too high for healthy skin**." Emphasis added.).

In other words, the art does not provide even a **reasonable expectation of success** that the claimed dosage could be attained with a controlled external x-ray beam that provides for the preferential destruction of tumor cells in a subject while localizing the damage so as not to severely injure the patient. Mills teachings with respect to a dosage administered by Mossbauer absorption with gamma radiation cannot provide a reasonable expectation of success with respect to a dosage administered by an external X-ray beam. In the absence of such reasonable expectation of success, the cited art is incompetent to set forth even a *prima facie* case of obviousness for the invention as claimed. See MPEP 2143.02.

The Examiner has dismissed the Cash teaching of the limit on x-ray dosage with the statement that "Cash does not rely on the release of Auger electrons for its therapeutic effects, but rather on the use of a contrast agent to stop more x-ray photons in the tumor than the amount stopped in the absence of contrast agent in healthy tissue" (official action of 15 April 2010 at page 6). However, a naked statement that Cash does not rely on Auger electrons does not negate the teaching in Cash that it is necessary to limit the dose of external x-ray radiation to prevent damage to healthy tissue, and it does not provide a reasonable expectation that this can be done with the use of line emission x-rays tuned to the K- or L-edge of the select compound that causes emission to the patient of a dose of 10^6 Gy.

The secondary reference cited by the Examiner cannot supplement the deficiencies in the primary reference even assuming for the sake of argument that the references were properly combinable. In particular, Wang does not show or suggest the use of line emission x-rays tuned to the K- or L- absorption edge of a select element to create an Auger cascade or that the same can be used selectively to destroy tumor cells **without destroying healthy tissue**.

SUMMARY AND CONCLUSION

For reasons discussed above, Appellant respectfully submits that the cited

references do not set forth even a *prima facie* case of obviousness for the invention defined by the claims of record.

Please charge Account No.12-0425 for any fees which may be due by this paper.

Respectfully submitted,

CLIFFORD J. MASS
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG.NO. 30086 (212) 708-1890

VIII. APPENDIX A - CLAIMS

1. A method for preferential disruption of malfunctioning cells in a living mammal, which comprises:

(a) administering a compound which associates with DNA in cells of said mammal, said compound comprising a pre-selected element selected from the group consisting of Pt, Ca, Ti, Br, I, Gd, Y and Ru; and then

(b) irradiating a selected region, in which malfunctioning cells having said compound associated with DNA are located, with line emission x-rays from an X-ray tube, said line emission X-rays being of an energy selected to cause emission of Auger electrons from said pre-selected element of said compound in a dose effective to disrupt DNA proximate to the irradiated pre-selected element, said dose for each activation of said X-ray tube being at least about 10^6 Gy localized with a distance of a few atomic diameters from the pre-selected element, said selected region being a localized region which predominantly contains the malfunctioning cells so as to localize the effects of disrupting DNA to the malfunctioning cells and to minimize the effect on normal cells.

3. A method according to claim 1, wherein the compound binds to the DNA.

5. A method according to claim 1, wherein the compound has an affinity for both normal and malfunctioning cells.

7. A method according to claim 1, wherein the compound has a selective affinity for malfunctioning cells.

12. A method according to claim 1, wherein the compound is cisplatin.

16. A method according to claim 1, wherein the compound is selected to have a high rate of excretion by normal physiological processes.

17. A method according to claim 1, wherein the compound is selected for stability against dissociation of the pre-selected element during the time prior to excretion or metabolism of the compound.

18. A method according to claim 1, wherein an end window transmission x-ray tube producing bright line emission x-rays is used for irradiating.

19. A method according to claim 18, wherein an e-beam generated in the x-ray tube is focused on a thin target having a thickness selected to provide the line_emission x-rays, said thickness not exceeding about 40 μm, said target being inside the tube and functions as part of the end window.

20. A method according to claim 19, wherein the target and the e-beam energy are selected to provide monochromatic line emission x-rays having an energy above and sufficiently near the K-absorption edge of the pre-selected element of the compound to cause said emission of Auger electrons.

21. A method according to claim 20, wherein the thin target is selected from the group consisting of Mo, Ag, La, Sr and Tm.

22. A method according to claim 19, wherein the target and the e-beam energy are selected to provide monochromatic line emission x-rays having an energy above and sufficiently near the L-absorption edge of the pre-selected element of the compound to cause said emission of Auger electrons.

23. A method according to claim 22, wherein the thin target is Rb.

24. A method according to claim 23, wherein the pre-selected element of the compound is Pt.

26. A method according to claim 1, wherein the dose of at least about 10^6 Gy is released

within a distance from the element of the compound of up to about 10 angstroms.

27. A method according to claim 1, wherein step (b) is repeated at least once.

28. A method according to claim 27, wherein Auger electrons are released during each repetition of step(b) with a dose of at least about 10^6Gy.

29. A method according to claim 28, wherein the dose of at least about 10^6 Gy is released within a distance from the element of the compound of up to about 10 angstroms.

30. A method according to claim 1, wherein step (b) is performed on cells removed from the mammal.

31. A method according to claim 30, wherein after step (b) is performed, the removed cells are returned to the mammal.

32. A method according to claim 30, wherein after step (b) is performed, the removed cells are transplanted.

33. A method according to claim 1, wherein step (a) and step (b) are performed on cells removed from the mammal.

34. A method according to claim 33, wherein after step (b) is performed, the removed cells are returned to the mammal.

35. A method according to claim 33, wherein after step (b) is performed, the removed cells are transplanted.

36. A method according to claim 1, wherein the malfunctioning cells are tumor or cancer cells and the mammal is a human.

38. A method according to claim 36, wherein the compound binds to the DNA.

40. A method according to claim 36, wherein the compound has an affinity for both normal and cancerous cells.

42. A method according to claim 36, wherein the compound has a selective affinity for cancerous cells.

47. A method according to claim 36, wherein the compound is Cisplatin.

51. A method according to claim 36, wherein the compound is selected to have a high rate of excretion by normal physiological processes.

52. A method according to claim 36, wherein the compound is selected for stability against dissociation of the pre-selected element during the time prior to excretion or metabolism of the compound.

53. A method according to claim 36, wherein an end window transmission x-ray tube producing bright line emission x-rays is used for irradiating.

54. A method according to claim 53, wherein an e-beam generated in the x-ray tube is focused on a thin target having a thickness selected to provide the line_emission x-rays, said thickness not exceeding about 40 μm, said target being inside the tube and functions as part of the end window.

55. A method according to claim 54, wherein the target and the e-beam energy are selected to provide monochromatic line emission x-rays having an energy above and sufficiently near the K-absorption edge of the element of the compound to cause said emission of Auger electrons.

56. A method according to claim 55, wherein the thin target is selected from the group consisting of Mo, Ag, La, Sr and Tm.

57. A method according to claim 54, wherein the target and the e-beam energy are

selected to provide monochromatic line emission x-rays having an energy above and sufficiently near the L-absorption edge of the pre-selected element of the compound to cause said emission of super electrons.

58. A method according to claim 57, wherein the thin target is Rb.

59. A method according to claim 58, wherein the pre-selected element of the compound is Pt.

61. A method according to claim 36, wherein the dose of at least about 10^6 Gy is released within a distance from the element of the compound of up to about 10 angstroms.

62. A method according to claim 36, wherein step (b) is repeated at least once.

63. A method according to claim 62, wherein Auger electrons are released during each repetition of step (b) with a dose of at least about 10^6 Gy.

64. A method according to claim 63, wherein the dose of at least about 10^6 Gy is released within a distance from the element of the compound of up to about 10 angstroms.

65. A method according to claim 1, wherein the malfunctioning cells are cancerous cells and the mammal is a human, wherein the method comprises:

(a) administering to the human the compound which associates with DNA, in cells of said human, said compound comprising a pre-selected element selected from the group consisting of Br, Ru, I, Gd and Pt; and then

(b) irradiating at least once, by means of an end window transmission x-ray tube, the selected region, in which the cancerous cells having said compound associated with DNA are located, with line emission x-rays of an energy selected to cause emission of Auger electrons from said pre-selected element of said compound in a dose effective to disrupt DNA proximate to the irradiated pre-selected element, said dose for each activation of said x-ray tube being at least about 10^6 Gy

within a distance from the pre-selected element of the compound of up to about 10 angstroms.

67. A method according to claim 65, wherein the compound binds to the DNA.

69. A method according to claim 65, wherein the compound has an affinity for both normal and tumorous cells.

71. A method according to claim 65, wherein the compound has a selective affinity for tumorous cells.

76. A method according to claim 65, wherein the compound is cisplatin.

77. A method according to claim 65, wherein the compound is selected to have a high rate of excretion by normal physiological processes.

78. A method according to claim 65, wherein the compound is selected from stability against dissociation of the pre-selected element time prior to excretion or metabolism of the compound.

79. A method according to claim 65, wherein an e-beam generated in the x-ray tube is focused on a thin target having a thickness selected to provide the line emission x-rays, said thickness not exceeding about 40 μm, said target being inside the tube and functions as part of the end window.

80. A method according to claim 79, wherein the target and the e-beam energy are selected to provide monochromatic line emission x-rays having an energy above and sufficiently near the K-absorption edge of the pre-selected element of the compound to cause said emission of Auger electrons.

81. A method according to claim 80, wherein the thin target is selected from the group consisting of Sr, Ag, La, and Tm.

82. A method according to claim 79, wherein the target and the e-beam energy are selected to provide monochromatic line emission x-rays having an energy above and sufficiently near the L-absorption edge of the pre-selected element of the compound to cause said emission of Auger electrons.

83. A method according to claim 82, wherein the thin target is Rb.

84. A method according to claim 83, wherein the pre-selected element of the compound is Pt.

85. A method for treating malfunctioning cells in a living mammal, which comprises:

(a) providing a kit comprising

(1) an x-ray tube having a target comprising a selected metal, said tube being capable of emitting monochromatic line emission x-rays; and (2) a compound comprising a selected element selected from the group consisting of Pt, Ca, Ti, Br, I, Gd, Y and Ru, said compound being capable, upon administration to said mammal, of associating with DNA in cells of said mammal; the selected metal of said target and the selected element of said compound being selected together:

(i) for said metal of said target to emit line emission x-rays having an energy above and near the K-absorption edge or the L-absorption edge of the selected element of said compound, and

(ii) for said element of said compound to release a dose of Auger electrons upon irradiation by said line emission x-rays in a dose effective to disrupt DNA proximate to the irradiated selected element, said dose for each activation of said X-ray tube being at least

about 10^6 Gy localized with a distance of a few atomic diameters from the pre-selected element;

(b) administering the compound to the mammal and

(c) irradiating a selected region, in which malfunctioning cells having said compound associated with DNA are located, with the monochromatic line emission x-rays form the x-ray tube to cause emission of Anger electrons from said pre-selected element of said compound in the dose effective to disrupt DNA proximate to the irradiated pre-selected element.

86. A method according to claim 85, wherein said x-ray tube is an end window transmission x-ray tube capable of emitting bright, line emission x-rays, said x-ray tube comprising an evacuated, elongated chamber having first and second ends, the first end being connected to a power supply, and within said chamber: electron emitter means near the first end for generating a beam of electrons; an end window transparent to x-rays at the second end, an inner portion of said end window comprising said target; and means for focusing said electron beam on said target.

87. A method according to claim 86, wherein the target has a thickness selected to provide the line emission x-rays, said thickness not exceeding about 40 μm.

88. A method according to claim 85, wherein the target is selected from the group consisting of Rb, Mo, Ag, La, Sr and Tm.

90. A method according to claim 85, wherein the compound has an affinity for both normal and malfunctioning cells.

97. A method according to claim 85, wherein the compound is cisplatin.

99. A method according to claim 85, wherein the pre-selected element of the compound is selected from the group consisting of Br, Ru, I, Gd and Pt.

IX. APPENDIX B - EVIDENCE

A declaration under 37 CFR 1.132 of C.G. Wang was filed 2 June 2009.

X. APPENDIX C - EVIDENCE

No related proceedings are referenced in section II above, hence copies of decisions in related proceeding are not provided.